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Unexplained Excess Risk of Bladder Cancer in Men

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In nearly all populations studied, the risk of bladder cancer is two to four times as great in men as in women. We estimated what the gender-specific incidence rates would be in the absence of exposure to known carcinogenic factors. The data used were obtained from interviews with 2,806 white individuals with bladder cancer and 5,258 white controls in the National Bladder Cancer Study and from incidence data for 1978 from the National Cancer Institute Surveillance, Epidemiology, and End Results Program. The total age-adjusted incidence of bladder cancer was 27.5 cases per 100,000 person-years for men and 7.0 for women, yielding a ratio of 3.9. Even in the absence of exposure to cigarettes, occupational hazards, or urinary tract infection, the gender-related risk persisted; the incidence of bladder cancer was 11.0 in men and 4.1 in women, yielding a ratio of 2.7. Possible explanations for the excessive risk in men include environmental and dietary exposures not yet identified and innate sexual characteristics such as anatomic differences, urination habits, or hormonal factors. [J Natl Cancer Inst 82:1636–1640, 1990]

Gender is among the most consistent and powerful predictors of the risk of developing bladder cancer. Throughout the world, the risk in men is two to four times higher than that in women (*1*). In the United States, the ratio of incidence in males to that in females is about 4, having risen from a ratio of 3 in 1947 (*2*). The incidence of bladder cancer is generally lower in less industrialized countries, as is the ratio of male-to-female incidence. One possible explanation for the differential risk in men is greater exposure to carcinogens in the environment, for example, different patterns of employment or of tobacco use. We used incidence statistics and interview data from a large, population-based, case-control study of bladder cancer conducted in 1978 in the United States to estimate the influence of the major known risk factors on the male-to-female ratio.

Materials and Methods

Data

Incidence rates for bladder cancer were derived from 10 population-based tumor registries and population estimates extrapolated from U.S. Census data for 1978 (*3*). The study area included five states (Connecticut, Iowa, New Jersey, New Mexico, and Utah) and five metropolitan areas (Atlanta, Detroit, New Orleans, San Francisco, and Seattle).

The prevalence of exposure to known carcinogens for bladder cancer and the associated relative risks were derived from the National Bladder Cancer Study, a collaborative, population-based, case-control study conducted in the same geographic areas in 1978 (*4*). We attempted to interview all residents aged 21–84 years who were first diagnosed with histologically confirmed bladder cancer during a 1-year period

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(the starting date varied among areas from December 1977 to March 1978). We identified 4,086 cases and interviewed 2,982 of these individuals (73%). To create a control group that was randomly chosen from the general population, we telephoned 22,633 households through random-digit dialing (5) and chose 2,928 household members aged 21–64; we also chose 4,057 people over the age of 64 years from the Health Care Financing Administration rosters. We interviewed 84% of the younger controls and 82% of the older controls.

The interviews were conducted in the home and lasted about 1 hour. Topics covered by the interview included demographic characteristics; tobacco use; consumption of tap water, coffee, alcoholic and other beverages, and artificial sweeteners; lifetime occupational and residential histories; hair dye use; history of diabetes; and history of urinary tract infections. Three of these were strong and relatively common risk factors: cigarette smoking, an occupational hazard, and one or more urinary tract infections. Smokers were defined as individuals who had smoked 100 or more cigarettes during their lifetime. Subjects were considered to have had a urinary tract infection if they reported a history of either a bladder or kidney infection. We considered as hazardous those jobs that had a relative risk of 1.5 or more or had a P value of .05 or less for the trend test for duration-response, among either white men or women. (Appendix I lists the job titles.) Detailed analyses of the exposures are available elsewhere (6–8). The year before interview was excluded in all assessments of exposure, and the analysis was restricted to white subjects (2,806 cases and 5,258 controls).

Analysis

We estimated several related parameters: the relative risk, which is the ratio of the incidence of bladder cancer within a group exposed to risk factors to the incidence within a comparable, unexposed group; the attributable proportion (or etiologic fraction, or percent attributable risk) in the population, which is the proportion of the incidence of bladder cancer that might be attributed to exposure to a given risk factor or factors; the estimated incidence of bladder cancer in an unexposed subgroup of the general population; and the male-to-female ratio of bladder cancer incidence. The attributable proportion in the population rises with the increase in either the relative risk or the proportion exposed. The complement of the attributable proportion (1–AP) multiplied by the incidence yields an estimate of what the incidence would be in the absence of exposure to the given risk factor. If the attributable proportions associated with exposure to a risk factor differ between men and women, the male-to-female ratios differ between the total population and the population unexposed to that risk factor.

Estimates of relative risk were adjusted for age and other confounding variables by stratification (9). We estimated the attributable proportion in the population (9), using as a baseline the experience of people unexposed to cigarettes, occupational hazards, or urinary tract infections. Only when a population unexposed to all three of these factors is used as the baseline can attributable proportions be compared with each other and added to yield the total fraction attributed to known causes. This method does not disaggregate the proportion attributable to each of two factors operating together. To calculate the age- and gender-specific incidence rates in the unexposed white population, we computed the fractions of cases and controls reporting no exposure to a risk factor in the interview. (This method assumes that non-respondents had the same exposure rates as respondents.)

Results

Most cases and controls had some exposure to a potentially hazardous job, smoked cigarettes, or reported a urinary tract infection (table 1). Overall, three fifths of white men and two fifths of white women (see % attributable proportion due to any exposure in table 1) appear to have developed bladder cancer because of exposure to one or more of these risk factors. The overlapping exposure to two risk factors, an occupational hazard and cigarette smoking, contributed greatly to the total incidence of bladder cancer among men (30% attributable proportion of total male incidence, table 1). For white men, cigarette smoking was a contributing risk factor in 57% of cases, and occupational hazards were a contributing factor in 43% of cases; however, 40% of cases involved both of these risk factors. Among white women, cigarette smoking contributed to 37% of cases and a urinary tract infection to 24% of cases.

Among white men, the overall inci-

Table 1. Estimated relative risks and population-attributable proportions for exposure to cigarette smoking, urinary tract infection, and high risk occupation*

Type of exposure	White men				White women			
	Control (%)	Cases (%)	RR	% AP	Control (%)	Cases (%)	RR	% AP
No exposures	13	5	1.0		30	17	1.0	
Cigarettes only	27	24	2.2	13	18	20	2.1	11
UTI only	2	1	1.5	0	16	12	1.4	3
Cigarettes, UTI	5	5	3.0	4	9	17	3.5	12
Job hazard only†	12	7	1.4	2	11	8	1.2	1
Jobs, cigarettes	34	43	3.1	30	7	11	2.7	7
Jobs, UTI	2	2	2.8	1	5	5	1.9	2
Jobs, cigarettes, UTI	5	12	5.6	10	5	9	3.7	7
Any exposure (95% CI)	87	95	2.7	60 (52-67)	70	83	2.0	42 (31-52)

*Abbreviations: RR = relative risk estimate adjusted for age; AP = attributable proportion in the general population; UTI = urinary tract infection; CI = confidence interval.

†Job hazard was defined as any job with a relative risk estimate, adjusted for age, of ≥ 1.5 or a trend test $P < .05$ for duration, in either sex.

dence of bladder cancer in 1978 was 27.5/100,000 person-years, 3.9 times as high as the rate in women (*3*). If the comparison is restricted to people unexposed to cigarettes, occupational hazards, or a urinary tract infection, the ratio falls to 2.7. The drop stems from the greater proportion of men who had smoked and held potentially hazardous jobs, partly offset by the greater proportion of women who had smoked and had at least one urinary tract infection.

Figure 1 shows the age-specific incidence rates in the U.S. population of white men and women aged 40-84 years and the corresponding incidence rates in the subpopulations of white men and women who were never exposed to cigarettes, occupational hazards, or a urinary tract infection. Unexposed men showed consistently higher rates of bladder cancer than unexposed women. Too few cases occurred among the population younger than 40 years of age to yield stable estimates of the rates of bladder cancer. The greater risk seen in men was not concentrated in particular age groups. Instead, the sex- and age-specific rates in the unexposed population roughly parallel those in the total population. Figure 1 also shows that the important effect of age does not solely reflect cumulative exposure to cigarettes, occupational hazards, or urinary tract infections. Furthermore, the parallel curves of the logarithm of incidence suggest that the effects of age and gender are roughly multiplicative, rather than additive.

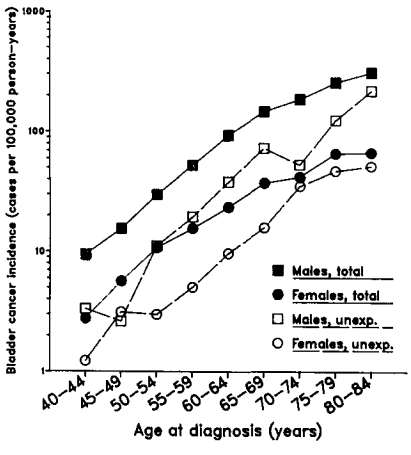

Figure 1. Incidence rates for bladder cancer among the white population in 1978. Rates are for total population and population unexposed to cigarette smoking, occupational hazards, and urinary tract infection.

Table 2. Estimated relative risks among white men and women (adjusted for age)

Relative risk factor*	White men			White women		
	Cases	Controls	RR	Cases	Controls	RR
Never smoked†	329	1,136	1.0	292	842	1.0
Ex-smoker (cigarettes/day)†						
< 20/day	186	478	1.3	71	104	2.0
20+/day	582	1,038	1.9	34	75	1.4
Smoker (cigarettes/day)†						
< 20/day	163	260	2.2	97	141	2.1
20-39/day	510	574	3.1	121	120	3.0
40+/day (trend test)	155	156	3.7	18	13	4.4
No UTI	1,689	3,363	1.0	388	900	1.0
One or more UTI (95% CI)	428	529	1.6 (1.4–1.9)	301	466	1.5 (1.2–1.8)
No job hazard	777	1,833	1.0	460	984	1.0
Any job hazard (95% CI)	1,340	2,059	1.5 (1.3–1.6)	229	382	1.2 (1.0–1.5)

*Relative risks for urinary tract infection and job hazard are adjusted for smoking; all relative risks are adjusted for age. Job hazard was defined as any job with an estimated relative risk, adjusted for age, of ≥ 1.5 or a trend test $P < .05$ for duration, in either sex. Abbreviations: UTI = urinary tract infection; CI = confidence interval.

†$P < .001$ in trend test for 6-level smoking variable.

We repeated the analysis with the definition of occupational risk broadened to include jobs that have been implicated in other studies but did not meet the stated criteria of elevated risk in our data (provided we found an estimated relative risk of at least 1.1). By this definition, only 2% of male cases occurred in men who had not been exposed to an occupational risk. The attributable proportion rose to 68% and 44% in men and women, respectively, so the male-to-female incidence ratio was affected very little. This ratio was also unaffected when we repeated the analysis and added high consumption of tap water (upper 40%) or artificial sweeteners (240 mg/day) as risk factors.

Relative risk estimates for each of the three key risk factors were generally similar in men and women; i.e., the risk from each of these factors roughly multiplies, rather than adds to, the underlying gender-specific risk, which is lower in women (table 2). The relative risk associated with occupational hazards was less than 1.5 in women because the jobs designated as hazardous included those with elevated risks in either men or women. Some of the jobs with a 50% or greater increase in risk for men carried less risk for women. Possible reasons for this finding include chance, the apparent hazard in men was spurious, or men and women with the same job title had different exposures.

Discussion

The excessive risk of bladder cancer in men as compared with women is seen in virtually all areas of the world and in all age groups. It applies mainly to transitional cell carcinomas, the most common of the bladder cancers, and less so to squamous cell carcinomas and adenocarcinomas (*10*). Our analysis suggests that the male-to-female risk ratio would indeed be reduced if men and women were equally exposed to cigarette smoking, occupational hazards, and urinary tract infections, but that nevertheless a large excess in risk for men compared with women would persist.

Several potential sources of error could have distorted our calculations of relative risks, attributable proportions, and the male-to-female incidence ratio among people unexposed to environmental carcinogens. Losses of information because of nonresponse and errors in recall (e.g., false-negative histories of urinary tract infections) could influence estimates of either exposure rates or relative risk. However, the estimates of relative risk are consistent with those seen from other studies. Furthermore, although misclassification inevitably dilutes estimates of relative risk, the comparison of attributable proportions in

men and women and the extrapolated male-to-female incidence ratio should be affected little because of the relative purity of the groups that lacked exposure according to these very broad, indeed overinclusive, definitions.

Perhaps a likelier source of error is that we omitted collecting data on some relevant exposures (i.e., additional risk factors that contribute to bladder cancer incidence). We omitted coffee drinking because its relationship to the risk of bladder cancer appears to be noncausal (*11*). Heavy use of analgesics containing phenacetin (30 or more days per year) increases risk but is an uncommon habit in the United States (*12*). Heavy use of artificial sweeteners (240 mg/day) was related to risk in these data but did not affect the male-to-female ratio because it was uncommon (*13*). Schistosomiasis, a contributor to squamous cell bladder cancer, is also rare in the United States. Consumption of tap water, usually chlorinated, was a risk factor in these data but did not affect the male-to-female incidence (i.e., risk) ratio because exposure was virtually identical in men and women (*14*). We lacked data to examine the recently suggested effects of diet (*15, 16*). Whether differences between men and women in micronutrient, fat, or meat intake affect the male-to-female incidence ratio should be examined in other studies. Wholly unsuspected risk factors, of course, could also affect the ratio.

Assuming this analysis has included the major environmental determinants of risk we do not know why men should have greater risk of bladder cancer even in the absence of these determinants. One possibility is greater urinary retention or stasis among men. One early report linked bladder cancer to urinary stasis due to prostatic lesions (*17*). A recent study (*18*) found an equal frequency of urination in men and women, but less concentrated urine in women. The association between the risk of bladder cancer and the frequency of urination has not been studied directly, but fluid intake has been examined, with equivocal results. In a population-based, case-control study performed in Denmark, the combined volume from coffee, tea, beer, and soft drinks was related to a moderate increase in risk (*19*). Total fluid intake was substantially greater among German patients with bladder cancer than among hospital controls, but controls were selected primarily from urology wards (*20*). In a population-based study in Utah, it was found that total fluid intake was not consistently related to risk (*21*).

A more likely explanation may be hormonal differences. One transplantable human bladder tumor cell line, R198, responds to hormones (*22,23*). The transplanted tumors grow poorly in the presence of estrogens but well in the presence of androgens. In addition, studies of rodents show that androgenic sex hormones cause the bladder to metabolize carcinogens differently, leading to greater potency of the carcinogen (*24,25*). Finally, androgen receptors occur in normal human bladder epithelium and are more numerous in bladder tumors and in tumors taken from men than in those in the same stage taken from women (*26*).

The multiplicative effects of gender and age and of gender and each of the three risk factors we studied may provide a clue to the role of gender in the etiology of bladder cancer. This interdependence of effects suggests a common biologic pathway. For example, the known environmental carcinogens, the unknown ones captured by the general effect of age, and hormonal effects may act at different stages of a multistage model of bladder carcinogenesis. Further attention to the effect of male hormones and other aspects of gender may yield insights into the origins and prevention of bladder cancer.

Appendix I

Standard occupational classification codes and job titles for occupations with relative risk ≥ 1.5 or duration-response trend test $P < .05$ in either men or women:

1033 Bootblacks
1050 Painters
1051 Painters and apprentices, construction and maintenance
1054 Painters, artistic, and sculptors
1082 Drivers, truck, delivery, and route
1083 Drivers, taxicabs, and chauffeurs
1125 Railroad switchmen
1170 Roofers and slaters
1232 Drill press operators
1235 Machine operators
1314 Punch and stamping press operators
1320 Metal fabrication, assembly, and repair
1322 Metal filers, polishers, sanders, and sand buffers
1433 Food counter and fountain workers
1450 Dishwashers
1470 Butchers (industry = 1111)
1502 Cement and concrete finishers
1503 Inspectors, graders, etc., in construction
1511 Salesmen of service, construction
1530 Blasters and powdermen
1611 Checkers and graders in manufacturing
1613 Manufacture laborers, NEC, weighers
1620 Cutting operatives
1665 Salespeople and salescheckers, NEC
1694 Lumbermen, raftsmen, etc.
1730 Agriculture science professors and technicians
1740 Gardeners, except farm (industry = 100)
1862 Writers, authors
1870 Telephone and telegraph operators
1900 Assessors, controllers
1941 Architects
2122 Chemical processing, NOS
2130 Primary aluminum processing workers
2141 Petroleum crude extraction workers
2153 Paperboard containers workers

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